

Ministry of Healthcare of Ukraine
Poltava State Medical University

**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in rheumatology clinic
<i>Study subject</i>	Management of the patients with fever Management of the patients with weight loss
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

1. The aims of the training course:

To Know:

1. Differential diagnosis the conditions that accompanied with the presence of prolonged fever.
2. Existing algorithms for diagnosis.
3. Test plan, the role of radiological, instrumental and laboratory methods of examination (radiography, bronhohrafy, CT, bronchoscopy, ultrasound, general and biochemical analysis, cultivation of blood, urine, bile, phlegm).
4. Tactic of patients depending.
5. Indications for consultation by other specialists (chest physician, oncologist, rheumatologists, infectious disease).
6. Drug treatment and non-medicamentous.

To be able to:

Conduct surveys and examination of patients with major Pulmonological syndromes

- draft examination of patients with major Pulmonological syndromes
- justify the use of basic diagnostic methods in pulmonology, identify indications and contraindications for their conduct, possible complications
- prescribe treatment, determine prognosis and to conduct primary and secondary prevention in the major respiratory diseases
- diagnose and assist in respiratory distress
- justify the need of pleural puncture
- Perform pikfluometry

Demonstrate knowledge of moral principles

The contents of topic:

Text

Introduction

Background

Fever of unknown origin (FUO) was defined in 1961 by Petersdorf and Beeson as the following: (1) a temperature greater than 38.3°C (101°F) on several occasions, (2) more than 3 weeks' duration of illness, and (3) failure to reach a diagnosis despite one week of inpatient investigation.¹

This article provides a review of the etiologies of FUO and a rational approach to investigating a patient with this interesting condition.

Pathophysiology

FUOs are caused by infections (30-40%), neoplasms (20-30%), collagen vascular diseases (10-20%), and numerous miscellaneous diseases (15-20%). The literature also reveals that between 5 and 15% of FUO cases defy diagnosis, despite exhaustive studies.

Variations in FUO, as found in the literature, reflect the populations and periods studied. In children, infections are the most common cause of FUO, whereas neoplasms and connective-tissue disorders are more common in elderly persons. FUOs that persist for more than one year are less likely to be caused by infections and neoplasms and much more likely to be due to granulomatous diseases (the most common cause in these cases).

Diagnostic advances continuously modify the spectrum of FUO-causing diseases; for example, serologic tests have reduced the importance of HIV and numerous rheumatic diseases (eg, systemic lupus erythematosus [SLE], juvenile rheumatoid arthritis [JRA], rheumatoid arthritis [RA]) as causes of FUO. Modern imaging techniques (eg, ultrasonography, CT scanning, MRI) enable early detection of abscesses and solid tumors that were once difficult to diagnose.

Patients with undiagnosed FUO (5-15% of cases) generally have a benign long-term course, especially when the fever is not accompanied by substantial weight loss or other signs of a serious underlying disease. These findings suggest that the underlying cause is one of the more serious diseases that initially manifest as FUOs. Such underlying diseases are usually diagnosed after an intensive and rational diagnostic evaluation.

Age

More than 30% of FUO cases in persons older than 50 years are related to connective-tissue disorders and vasculitic disorders. Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are the two principal connective-tissue etiologies, accounting for 50% of the cases.

Clinical

History

- Diagnostic approach to fever of unknown origin (FUO) in adults
 - Inquire about symptoms involving all major organ systems, including a detailed history of general symptoms (eg, fever, weight loss, night sweats, headaches, rashes).
 - Record all symptoms, even if they disappeared before the examination. Previous illnesses are important, including surgeries and psychiatric illnesses.
 - Provide a detailed evaluation including the following:
 - Family history
 - Immunization status
 - Occupational history
 - Travel history
 - Nutrition (including consumption of dairy products)
 - Drug history (over-the-counter medications, prescription medications, illicit substances)
 - Sexual history
 - Recreational habits
 - Animal contacts (including possible exposure to ticks and other vectors)

Physical

- Definitive documentation of fever and exclusion of factitious fever are essential early steps in the physical examination.
 - Measure the fever more than once and in the presence of a nurse to exclude manipulation of thermometers.
 - Electronic thermometers facilitate the rapid and unequivocal documentation of fever.
- The pattern of fever (continuous, remittent, intermittent) is usually of little help in the evaluation.
 - In general, specific fever patterns do not correlate strongly with specific diseases. Notable exceptions include tertian and quartan malaria. However, most people who are naive about malaria are not diagnosed with FUO because they are usually diagnosed with malaria before 3 weeks have elapsed.
 - Other diseases (eg, brucellosis, borreliosis, Hodgkin disease) tend to cause recurrent episodes of fever.

- Repeat a regular physical examination daily while the patient is hospitalized. Pay special attention to rashes, new or changing cardiac murmurs, signs of arthritis, abdominal tenderness or rigidity, lymph node enlargement, fundoscopic changes, and neurologic deficits.

Causes

- Bacterial diseases
 - Abscesses: FUO should prompt consideration of abscesses, which are usually located intra-abdominally, even in the absence of localizing symptoms. Previous abdominal operations, trauma, or histories of diverticulosis, peritonitis, endoscopy, and gynecologic procedures increase the likelihood of an occult intra-abdominal abscess. The most common abscess locations include the subphrenic space, liver, right lower quadrant, retroperitoneal space, and the female pelvis.
 - Tuberculosis (TB): This is usually considered in the FUO differential diagnoses²; however, several factors may prevent a prompt diagnosis of TB. Dissemination, which usually occurs in immunocompromised patients, may initially manifest as constitutional symptoms that lack localizing signs. Chest radiography findings may be normal. Results from purified protein derivative (PPD) tests may be negative, and culture findings may not become positive for 4-6 weeks. TB of the kidney or mesenteric lymph nodes tends to manifest as FUO by lacking characteristic localized manifestations. Disseminated visceral infections with atypical mycobacteria (*Mycobacterium avium* being the prototype) also cause FUO; however, most of these patients have some other underlying hematologic malignancy or are infected with HIV.
 - Urinary tract infections (UTIs): These rarely cause FUO because urinalysis is an easily performed routine test that is used to detect most cases of UTIs. However, in young children, the collection of clean-catch urine specimens may be difficult; furthermore, perinephric abscesses occasionally fail to communicate with the urinary system, resulting in normal urinalysis findings. Occult UTI is possible in a patient with anatomic abnormalities of the urinary tract and FUO.
 - Endocarditis: This is now a rare cause of FUO. Failure to diagnose endocarditis may be due to the absence of a murmur or the failure of blood cultures to yield the organism. Culture-negative endocarditis is reported in 5-10% of endocarditis cases. Prior antibiotic therapy is the most common reason for negative blood cultures.
 - Hepatobiliary infections: In patients with hepatobiliary infections, cholangitis can occur without local signs and with only mildly elevated or normal findings on liver function tests. Similarly, acute cholecystitis and gallbladder empyema can lead to a diagnosis of FUO because of the lack of right upper quadrant pain or jaundice, especially in elderly patients.
 - Osteomyelitis: This usually causes localized pain or discomfort, at least intermittently. The most common reason for misdiagnosis of osteomyelitis is the failure to consider the disease in a patient who is febrile with musculoskeletal symptoms. Consider vertebral osteomyelitis in patients with low-grade fever or a history of UTIs. Radiographs may not show changes for weeks after the development of symptoms. Radionuclide studies (technetium Tc 99m bone scanning) are more sensitive than plain radiography, and MRI is also an extremely useful test for the diagnosis of osteomyelitis.
 - Rickettsia: Chronic infections with *Coxiella burnetii*, chronic Q fever, and Q fever endocarditis have been identified in patients with FUO. Signs of hepatic involvement are common, and the infection is transmitted from cattle and sheep. Perform serologic tests in suspected cases.³
 - Chlamydia: Consider *Chlamydia psittaci* infection, the cause of psittacosis, in patients with FUO who have a history of contact with birds. On rare occasions, *Lymphogranuloma venereum* infection manifests as FUO. Serology is essential for the diagnosis of these chlamydial infections.

- Systemic bacterial illnesses: Some systemic bacterial illnesses can manifest as FUOs. Brucellosis, still prevalent in Latin America and the Mediterranean, is very important. Consider this disease in patients with persistent fever and a history of contact with cattle, swine, goats, and/or sheep or in patients who consume raw milk products. Researchers have also described systemic infections with *Salmonella* species, *Neisseria meningitidis*, and *Neisseria gonorrhoeae* as causes of FUO. Cutaneous changes may be the only sign other than fever in neisserial infections. Cultures and serologic tests establish the diagnosis of these infections.
 - Spirochetal diseases: The most important spirochete is *Borrelia recurrentis*, which is transmitted by ticks and is responsible for sporadic cases of relapsing fever. Rat-bite fever (*Spirillum minor*), Lyme disease (*Borrelia burgdorferi*), and syphilis (*Treponema pallidum*) are other spirochetal diseases that can cause FUO.
- Viral diseases
 - HIV: Prolonged febrile episodes are common in patients with advanced HIV infection. Approximately 75% of the cases are infectious in nature, about 20-25% are due to lymphomas, and a small fraction (0-5%) are due to HIV itself. Typical and atypical mycobacteria and cytomegalovirus (CMV) are opportunistic infections that frequently cause prominent constitutional symptoms, including fever, with few localizing or specific signs. Other opportunistic infections (eg, salmonellosis, histoplasmosis, toxoplasmosis) can also present as FUO and elude rapid diagnosis in patients who are febrile with AIDS.
 - AIDS: More than 80% of patients with AIDS and lymphomas have involvement of extranodal sites (usually the brain). However, lymphomas are occasionally difficult to diagnose promptly. Perform extensive diagnostic workup studies (eg, imaging studies) to exclude these opportunistic diseases in patients with HIV fever who have a prolonged fever before attributing the fever to the HIV infection.
 - Herpes viruses: CMV and Epstein-Barr virus (EBV) can cause prolonged febrile illnesses with constitutional symptoms and no prominent organ manifestations, particularly in elderly persons. Infections with these viruses usually cause lymphadenopathies, which may be missed on physical examination if the lymph nodes are not prominently enlarged. Serologic testing can confirm the correct diagnosis when the patient presents with lymphocytosis with atypical lymphocytes. The results of these tests may initially be negative; therefore, repeat them in suspected cases 2-3 weeks after the onset of illness.
- Fungal infections: Immunosuppression, the use of broad-spectrum antibiotics, the presence of intravascular devices, and total parenteral nutrition all predispose to disseminated fungal infections, and *Candida albicans* is the main culprit. Systemic infection may remain undiscovered in these patients because blood cultures are negative in approximately 50% of the cases. *Malassezia furfur* infection can cause FUO and skin infections in patients on total parenteral nutrition who receive intravenous lipid preparations. In some cases, fever is the most prominent symptom in patients with reticuloendothelial involvement by histoplasmosis without clinical manifestations in other organs.
- Parasitic infections: Consider toxoplasmosis in patients who are febrile with lymph node enlargement; however, the diagnosis may be difficult to establish because the lymph nodes may be small. Rising antibody titers and immunoglobulin M (IgM) antibodies confirm the diagnosis. If the physician is unaware of a history of recent travel to an endemic area and if the fever pattern is nonsynchronized, malaria can be missed as a cause of fever. Other parasites that cause FUO in rare cases include *Trypanosoma*, *Leishmania*, and *Amoeba* species.
- Neoplasms
 - Lymphomas: Hodgkin and non-Hodgkin lymphomas frequently cause fever, night sweats, and weight loss. The correct diagnosis can be delayed if the tumor is difficult to detect (eg, when the disease is confined to the retroperitoneal lymph nodes). Anemia may be the most prominent laboratory abnormality.

- Leukemias: Acute leukemias are another important neoplastic group that can cause FUO. In preleukemic states, the peripheral blood smear and bone marrow aspirate may not reveal the correct diagnosis; therefore, perform a bone marrow biopsy.
- Solid tumors: Among solid tumors, renal cell carcinoma is most commonly associated with FUO, with fever being the only presenting symptom in 10% of cases. Hematuria may be absent in approximately 40% of cases, whereas anemia and a highly elevated sedimentation rate are common.
- Other solid tumors: Solid tumors such as adenocarcinomas of the breast, liver, colon, or pancreas and liver metastases from any primary site may manifest as fever.
- Malignant histiocytosis: This is a rare rapidly progressive malignant disease that manifests as high fevers, weight loss, enlarged lymph nodes, and hepatosplenomegaly. It is an occasional cause of FUO.
- Collagen vascular and autoimmune diseases
 - Collagen vascular and autoimmune diseases can manifest as FUO if the fever precedes other more specific manifestations (eg, arthritis, pneumonitis, renal involvement).
 - SLE was a relatively common cause of FUO 20 years ago; currently, it is readily diagnosed in most cases by the demonstration of antinuclear antibodies.
 - Systemic-onset JRA is a cause of FUO and is often difficult to diagnose. High-spiking fevers, nonpruritic rashes, arthralgias and myalgias, pharyngitis, and lymphadenopathy are common. Laboratory abnormalities include pronounced leukocytosis, an elevated erythrocyte sedimentation rate (ESR), anemia, and abnormal liver function tests. These findings usually trigger a search for an infectious cause; thus, they delay the correct diagnosis.
 - Consider polyarteritis nodosa (PAN), RA, and mixed connective-tissue diseases (ie, other collagen vascular diseases) because of their potential for nonspecific presentations. Rheumatic fever can be difficult to diagnose because it is rare in the developed world.
- Granulomatous diseases
 - Sarcoidosis: Given its multiorgan involvement, sarcoidosis rarely manifests as fever and malaise without evidence of lymph node and pulmonary involvement. Erythema nodosum is occasionally present, and the finding of noncaseous granulomas in the liver should raise concern.
 - Regional enteritis: Crohn disease is the most common gastrointestinal cause of FUO. Diarrhea and other abdominal symptoms are occasionally absent, particularly in young adults. The diagnosis is established with endoscopy and biopsy.
 - Granulomatous hepatitis: In some patients with hepatic granulomas, none of the diseases usually associated with FUO (eg, TB, syphilis, brucellosis, sarcoidosis, Crohn disease, Hodgkin disease) are found. These patients often have fever that may be accompanied by slight hepatomegaly, asthenia, and, sometimes, arthralgias and myalgias for many months or years. An elevated alkaline phosphatase level is the most consistent laboratory abnormality. The long-term prognosis is excellent; approximately 50% of patients recover spontaneously, and the other 50% respond to corticosteroid treatment (duration of therapy ranging from a few weeks to several years).
- Drug fever: Although a wide variety of drugs can cause drug fever, the most common are beta-lactam antibiotics, procainamide, isoniazid, alpha-methyldopa, quinidine, and diphenylhydantoin. A history of allergy, skin rashes, or peripheral eosinophilia is often absent in cases of drug fever. Neither the fever pattern nor the duration of previous therapy is helpful in establishing the diagnosis. When suspecting drug fever, discontinue the implicated drug. Stopping the causative drug generally leads to defervescence within 2 days
- Inherited diseases: In patients of Mediterranean descent with FUO, familial Mediterranean fever is most often the cause. Recurrent febrile episodes at varying intervals are associated with pleural, abdominal, or joint pain due to polyserositis. This is a diagnosis of exclusion.
- Endocrine disorders

- Hyperthyroidism and subacute thyroiditis⁴ are the 2 most common endocrinologic causes of FUO. In fact, fever is often the major clinical sign, in addition to weight loss.
 - Adrenal insufficiency is a rare, potentially fatal, very treatable endocrine cause of FUO. Consider this diagnosis in patients with nausea, vomiting, weight loss, skin hyperpigmentation, hypotension, hyponatremia, and hyperkalemia.
- Peripheral pulmonary emboli and occult thrombophlebitis: These have been known to cause FUO. Consider these diagnoses in patients with predisposing conditions, particularly previous surgery, traumas, or prolonged bed rest. Another possible cause of fever after surgery or trauma is an undiscovered hematoma, usually located intra-abdominally.
- Kikuchi disease: A self-limiting necrotizing lymphadenitis known as Kikuchi disease was recently described as a cause of FUO. Kikuchi disease causes prolonged fever, constitutional symptoms, laboratory evidence of chronic inflammation, and, sometimes, liver function abnormalities. The etiology of Kikuchi disease is unknown.
- Factitious fever: This is responsible for as many as 10% of FUO cases in some series and is most commonly encountered among young adults with health care experience or knowledge. Evidence of psychiatric problems or a history of multiple hospitalizations at different institutions is common. Rapid changes of body temperature without associated shivering or sweating, large differences between rectal and oral temperature, and discrepancies between fever, pulse rate, or general appearance are typically observed among patients who manipulate or exchange their thermometers, the most common cause of factitious fever. Alternatively, fever may be caused by injection of nonsterile material (eg, feces, milk), resulting in atypically localized abscesses or polymicrobial infections. Therefore, consider factitious fever as a possibility in every patient with prolonged fever, especially in patients with one or more of the features described.
- Other vasculitides
 - Giant cell arteritis
 - Classic symptoms of GCA include temporal headache, jaw claudication, fever, visual disturbances (visual loss, blurred vision, diplopia, amaurosis fugax), weight loss, anorexia, fatigue, and cough. Polymyalgia (aching and stiffness of the proximal muscles and the trunk) occurs in 40% of these patients. During the examination, the physician may observe temporal artery tenderness or decreased pulsation. Laboratory findings include an elevated ESR, mild-to-moderate normochromic normocytic anemia, elevated platelet counts, and abnormal liver function tests (25% of cases). Perform a biopsy of a temporal artery to obtain a definitive diagnosis. Pathologic review shows vasculitis and a mononuclear cell infiltrate.
 - Treat the patient with high doses of steroids, and use intravenous steroids if the patient is very ill or has significant ocular compromise. Carefully monitor the patient because inadequate treatment and steroid toxicities (eg, hypertension, diabetes, dyspepsia, bone loss, psychosis, cataracts) can cause significant morbidity.
 - Polymyalgia rheumatica
 - PMR is characterized by symmetrical pain and stiffness involving the lumbar spine and large proximal muscles, most notably the neck, shoulders, hips, and thighs. Symptoms are usually worse in the morning. Constitutional symptoms (eg, fever, malaise, depression, weight loss) are also observed. Symptoms may worsen relentlessly over weeks to months without treatment. Physical examination is notable for normal muscle strength. Carefully perform a history and physical examination because such protean symptoms may evade diagnosis.
 - The diagnosis of PMR is clinical, and treatment is 2-fold, consisting of (1) amelioration of symptoms with steroid therapy and (2) close monitoring for possible development of GCA.

- PAN: This ranks a distant third behind GCA and PMR among the vasculitides that cause FUO in patients older than 50 years. PAN involves the medium- and small-sized muscular arteries. The male-to-female incidence ratio is 2:1. Incidence increases in patients with hepatitis B or C. Any 3 of the following 10 findings is sufficient for the diagnosis of PAN (sensitivity 82%, specificity 86%), and therapy consists of prednisone (cyclophosphamide is used in refractory cases):
 - Mononeuritis multiplex
 - Myalgias with muscle tenderness
 - Livedo reticularis
 - Testicular pain or tenderness
 - Renal impairment (elevated BUN and creatinine levels)
 - Weight loss of 4 kg or more
 - Diastolic blood pressure greater than 90 mm Hg
 - Hepatitis B positive
 - Arteriography showing small and large aneurysms and focal constrictions between dilated segments
 - Biopsy of small- or medium-sized arteries containing white blood cell infiltrate
- Other vasculitides that cause FUO include Wegener granulomatosis, Takayasu arteritis, and cryoglobulinemia. These are uncommon causes of FUO.

Differential Diagnoses

Abdominal Abscess	Gout
Actinomycosis	Graft Versus Host Disease
Acute Bacterial Prostatitis and Prostatic Abscess	Graves Disease
Acute Lymphoblastic Leukemia	HACEK Group Infections
Acute Myelogenous Leukemia	Haemophilus Influenzae Infections
Acute Respiratory Distress Syndrome	Hairy Cell Leukemia
Acute Rheumatic Fever	Hepatic Carcinoma, Primary
Adenoviruses	Hepatitis A
Adrenal Carcinoma	Hepatitis B
Adrenal Crisis	Hepatitis C
Amebiasis	Hepatitis D
Amebic Hepatic Abscesses	Hepatitis E
Appendicitis	Hepatorenal Syndrome
Arenaviruses	Herpes Simplex
Arthritis as a Manifestation of Systemic Disease	Herpes Zoster
Ascariasis	Histoplasmosis
Aspergillosis	HIV Disease
Atelectasis	Hookworms
Atrial Myxoma	Human Herpesvirus Type 6
Bacillary Angiomatosis	Hypersensitivity Pneumonitis
Bacteroides Infection	Hyperthyroidism
Balantidiasis	Inflammatory Bowel Disease
Bartonellosis	Influenza
Blastomycosis	Injecting Drug Use
Botulism	Interstitial Cystitis
Brain Abscess	Intestinal Flukes

Breast Cancer
Bronchiectasis
Bronchitis
Brucellosis
California Encephalitis
Campylobacter Infections
Candidiasis
Carcinoid Lung Tumors
Carcinoid Tumor, Intestinal
Cardiac Neoplasms, Primary
Catscratch Disease
Celiac Sprue
Cellulitis
Cerebral Aneurysm
Chagas Disease (American Trypanosomiasis)
Chancroid
Chlamydial Genitourinary Infections
Chlamydial Pneumonias
Cholangitis

Cholecystitis
Choledocholithiasis
Cholelithiasis
Chronic Bacterial Prostatitis
Chronic Lymphocytic Leukemia
Chronic Mesenteric Ischemia
Chronic Myelogenous Leukemia
Clostridial Cholecystitis
Clostridial Gas Gangrene
Collagenous and Lymphocytic Colitis
Colon Cancer, Adenocarcinoma
Corynebacterium Infections
Coxsackieviruses
Cryptococcosis
Cryptosporidiosis
Cysticercosis
Cytomegalovirus
Cytomegalovirus Colitis
Cytomegalovirus Esophagitis
Dengue Fever
Diabetic Ulcers
Dipylidiasis
Diverticulitis
Eastern Equine Encephalitis
Ebola Virus

Intra-abdominal Sepsis
Japanese Encephalitis
Klebsiella Infections
Legionnaires Disease
Leishmaniasis
Leptospirosis
Leukocytoclastic Vasculitis
Libman-Sacks Endocarditis
Listeria Monocytogenes
Liver Abscess
Lung Abscess
Lyme Disease
Lymphocytic Choriomeningitis
Lymphocytic Interstitial Pneumonia
Lymphogranuloma Venereum (LGV)
Lymphoma, Diffuse Large Cell
Lymphoma, Diffuse Mixed
Lymphoma, Follicular
Lymphoma, High-Grade Malignant Immunoblastic
Lymphoma, Lymphoblastic
Lymphoma, Malignant Small Noncleaved
Lymphoma, Mantle Cell
Lymphoma, Mediastinal
Lymphoma, Non-Hodgkin
Malaria
Malignant Carcinoid Syndrome
Mastocytosis, Systemic
Mediastinitis
Mediterranean Fever, Familial
Mediterranean Spotted Fever
Meningitis
Meningococcal Infections
Meningococcemia
Microsporidiosis
Miliary Tuberculosis
Mixed Connective-Tissue Disease
Molluscum Contagiosum
Mucormycosis
Multisystem Organ Failure of Sepsis
Mycoplasma Infections
Mycosis Fungoides
Myocarditis
Naegleria Infection
Nematode Infections

Echoviruses
Emphysema
Emphysematous Cholecystitis
Emphysematous Pyelonephritis
Empyema, Gallbladder

Empyema, Pleuropulmonary
Enterobacter Infections
Enterococcal Infections
Enteroviruses
Eosinophilic Pneumonia
Epididymal Tuberculosis
Epididymitis
Epidural Abscess
Erythema Multiforme (Stevens-Johnson Syndrome)
Escherichia Coli Infections
Foreign Body Aspiration
Gardnerella
Gas Gangrene
Gastroenteritis, Bacterial
Gastroenteritis, Viral
Giant Cell Arteritis
Giardiasis
Glomerulonephritis, Nonstreptococcal Associated With Infection
Glomerulonephritis, Poststreptococcal
Goiter
Goiter, Diffuse Toxic
Goiter, Toxic Nodular
Gonococcal Arthritis
Gonococcal Infections

Other Problems to Be Considered

Atypical mycobacterial infection
Bubonic plague
Clostridial necrotizing fasciitis
Eosinophilic toxocariasis
Fungal infections of the genitourinary tract
Gallbladder gangrene
Heroin abuse
Lung cancer
Lyssavirus infection
Picornavirus infection
Pneumoconiosis
Retroviral infections
Rhinoencephalomyelitis
Sepsis
Sphenoid sinusitis
Thrombophlebitis

Neuroleptic Malignant Syndrome
Neutropenia
Neutropenic Enterocolitis
Nocardiosis
Nonarticular Rheumatism/Regional Pain Syndrome
Nonbacterial Prostatitis
Norwalk Virus
Onchocerciasis
Orbivirus
Pancreatitis, Acute
Pelvic Inflammatory Disease
Pericarditis, Acute
Pericarditis, Constrictive
Pericarditis, Constrictive-Effusive
Pericholangitis
Pharyngitis, Bacterial
Pharyngitis, Viral
Pinworm
Pneumococcal Infections
Pneumonia, Bacterial
Pneumonia, Fungal
Pneumonia, Viral
Proctitis and Anusitis

Psittacosis
Q Fever
Recurrent Pyogenic Cholangitis

Thyroid carcinoma
Trypanosoma infection
TB of the genitourinary tract
UTI
Venereal warts
Osteomyelitis
Rat-bite fever (*S minor*)
Malassezia furfur infection
C burnetii infection
Malignant histiocytosis
Drug fever
Factitious fever
Kikuchi disease

Workup

Laboratory Studies

- CBC count and microscopic examination
 - Anemia is an important finding and suggests a serious underlying disease.
 - Ensure that leukemias are not missed in aleukemic or preleukemic cases.
 - Suspect herpesvirus infection if the patient has lymphocytosis with atypical cells.
 - A leukocytosis with an increase in bands suggests an occult bacterial infection.
 - Diagnose malaria and spirochetal diseases with the aid of direct examination of the peripheral blood smear; however, repeated examinations are often necessary.
- Urinalysis: Exclude UTIs and malignant tumors of the urinary tract; however, not all of them are consistently associated with pathologic findings in the urine.
- Serum chemistry
 - At least one liver function test result is usually abnormal, with an underlying disease originating in the liver or a disease that causes nonspecific alterations of the liver (eg, granulomatous hepatitis).
 - Most other chemistry tests rarely contribute to the diagnosis, although they are frequently ordered.
- Cultures
 - Blood cultures for aerobic and anaerobic pathogens are essential in the evaluation; however, no more than 6 sets of blood cultures are required. Routinely culture the patients' urine.
 - Cultures of sputum and stool may be helpful in the presence of signs or symptoms suggestive of pulmonary or gastrointestinal disease, respectively.
 - Obtain cultures for bacteria, mycobacteria, and fungi in all normally sterile tissues and liquids that are sampled during further workup. These tissues and fluids include cerebrospinal fluid (CSF), pleural or peritoneal fluid, and fluid from the liver, bone marrow, and lymph nodes.
- Serologies
 - Serologies are most helpful if paired samples show a significant, usually 4-fold, increase of antibodies specific to an infectious microorganism. Brucellosis, CMV infection, infectious mononucleosis, HIV infection, amebiasis, toxoplasmosis, and chlamydial diseases are diagnosed with serology.
 - These diagnostic tests are of limited value in most patients with fever of unknown origin (FUO), but they are appropriate for evaluation of the above illnesses in the correct clinical and epidemiological setting.
- Other tests
 - Frequently check antinuclear antibody (ANA) titers, rheumatologic factor, thyroxine level, and ESR because they are helpful in diagnosing certain conditions (lupus, RA, thyroiditis,

hyperthyroidism, GCA, PMR). Their diagnostic accuracy is limited in other autoimmune and collagen vascular diseases.

- In patients in whom GCA and PMR are suspected, checking the ESR may be particularly useful because the ESR is nearly always greater than 60 mm/h (and often is much higher, especially in GCA).

Imaging Studies

- Chest radiography: Routinely obtain chest radiography.
- Abdominal ultrasonography: Routine abdominal ultrasonography may also be justified, even in the absence of signs of an intra-abdominal process. However, negative ultrasonographic findings and absent symptoms suggestive of an intra-abdominal process do not exclude such a process.
- CT scanning
 - If ultrasonography fails to help reveal the diagnosis, obtain CT scans of the abdomen in all patients with symptoms suggesting an intra-abdominal process, in patients with suspected retroperitoneal tumors or infections, and in those with abnormal findings on liver function tests.
 - Intravenous pyelography may be more sensitive than CT scanning in detecting processes involving the descending urinary tract, but CT scanning is preferred for most other processes of the retroperitoneal space.
- MRI: This can be very useful when osteomyelitis is suspected. MRI has also been used in the diagnosis of vasculitides.

Other Tests

- Endoscopic examination
 - Perform an endoscopic examination of the upper and lower gastrointestinal tract, including retrograde cholangiography when indicated or when searching for Crohn disease, Whipple disease, biliary tract disease, and gastrointestinal tumors.
 - Occasionally, complementing endoscopic studies with barium enemas or upper gastrointestinal series is necessary.
- Radionuclide studies
 - Perform ventilation and perfusion radionuclide studies to document pulmonary emboli.
 - Obtain a pulmonary angiography when suspecting pulmonary emboli, despite negative scanning studies.
 - A technetium bone scan may be a more sensitive method for documenting skeletal involvement when suspecting osteomyelitis in a patient without compatible changes in conventional radiography.
 - Consider radionuclide studies using gallium citrate or granulocytes labeled with indium In 111 for diagnosis of occult abscesses, neoplasms, or soft-tissue lymphomas.
- Positron emission tomography (PET) scanning: This has enhanced the detection of occult neoplasms, lymphomas, and vasculitides in patients with FUO.
- Echocardiography: This technique is highly sensitive in diagnosing endocarditis, particularly when transesophageal echocardiography is available.

Procedures

- The final diagnosis is obtained during direct biopsy examination of involved tissue. Biopsies are easily performed in enlarged accessible lymph nodes, other peripheral tissues, and bone marrow.
- The decision to biopsy is more difficult if it necessitates an exploratory surgical procedure (eg, laparotomy). This is rarely indicated (eg, when imaging techniques are nondiagnostic and an intra-abdominal source is suspected).

- Liver biopsy rarely yields helpful data in patients without abnormal liver function tests or abnormal liver findings (observed on CT scan or ultrasonography).

Treatment

Medical Care

- In general, empiric therapy has little or no role in cases of classic fever of unknown origin (FUO).
- Treatment should be directed toward the underlying cause, as needed, once a diagnosis is made.
- Some studies suggest a few exceptions to this general approach, including the following:
 - Cases that meet criteria for culture-negative endocarditis
 - Cases in which findings or the clinical setting suggests cryptic disseminated TB (or, occasionally, other granulomatous infections)
 - Cases in which temporal arteritis with vision loss is suspected.
- Several studies have found that prolonged undiagnosed FUO generally carries a favorable prognosis.

Surgical Care

Because of a better understanding of the etiologies and careful diagnostic approaches, patients with FUO rarely need surgical treatment.

Consultations

Appropriate consultations are indicated based on patient history, physical examination, laboratory data, and radiologic findings, including the following:

- Infectious disease specialist
- Hematologist/oncologist
- Rheumatologist
- Pulmonologist
- Gastroenterologist
- Endocrinologist
- Interventional radiologist
- Surgeon

Medication

The medications used depend on the etiology of the fever of unknown origin (FUO).

Follow-up

Further Inpatient Care

- Approximately 5-15% of patients with fever of unknown origin (FUO) remain undiagnosed, even after extensive evaluations.
- Careful review of the literature shows that patients with FUO usually have a benign long-term course, especially in the absence of substantial weight loss or other signs of a serious underlying disease.
- No evidence supports prolonged hospitalization in patients who are clinically stable and whose workup findings are unrevealing.

Further Outpatient Care

- Conduct close follow-up procedures and systematic re-evaluation studies to prevent clinical worsening. Guide further workup studies on an outpatient basis.

Inpatient & Outpatient Medications

- The medications used to treat FUO are case-dependent.

Transfer

- Indications for transfer include the following:
 - The current facility is unable to establish a diagnosis,
 - Diagnostic tests are unavailable at the existing facility,
 - The patient deteriorates clinically.

Complications

- Complications of FUO, if they occur, are case dependent.

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Prognosis

- The prognosis of FUO depends on the underlying cause and varies from patient to patient.

Recommended literature:

I. Main:

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).
2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.
3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у 3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічна дія ліків – Side Effects of Medications: навчальний посібник у 2 т. / заг. ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.

7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

II. Additional literature:

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. -Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook fur medical students / Ye. Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143 .
7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).